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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,339	08/15/2001	Luet Lok Wong	P02196USO	7723

26271 7590 04/21/2006  
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EXAMINER
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PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/856,339

Applicant(s)

WONG ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 February 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 3,5 and 22-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3,5 and 22-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This application is a 371 of PCT/GB99/03873.

The amendment filed on February 1, 2006, canceling claim 2 and amending claims 3, 5 and 25, has been entered.

Claims 3, 5 and 22-25 are pending and are under consideration.

### ***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, page 7 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### ***Response to Arguments***

Applicant's amendment and arguments filed on February 1, 2006, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 3, 5 and 25 and claims 22-24 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 5 and 25 recite the terms "P450cam" and "P450BM-3". The metes and bounds of the terms in the context of the claims are unclear. Reciting the full name of the enzyme would overcome the rejection.

Claims 25 and claims 3, 5 and 22-24 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the limitation "the substituent" in line 3. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 5 and 22-25 are drawn to a method of oxidizing limonene, pinene or cyclic sesquiterpenes with A) variants of a P450cam of SEQ ID NO:1, wherein said

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variant comprises one or more substitutions at positions 87, 96, 244, 247 or 248 of SEQ ID NO:1 or B) variants of a P450BM-3 of SEQ ID NO:24, wherein said variant comprises one or more substitutions at positions 47, 51, or 87 of SEQ ID NO:24.

Further, the claims are not limited to variants of SEQ ID NO:1 consisting of the substitutions at positions 87, 96, 244, 247 or 248, but to any variant of SEQ ID NO:1 comprising the recited substitutions and any other modifications. Similarly, the claims are not limited to variants of SEQ ID NO:24 consisting of the substitutions at positions 47, 51, or 87, but to any variant of SEQ ID NO:24 comprising the recited substitutions and any other modifications. Therefore, the claims are drawn to a method of oxidizing limonene, pinene or cyclic sesquiterpene using a genus of polypeptides having any structure. The specification only describes a method of a method of oxidizing limonene, pinene or cyclic sesquiterpene using a variant of SEQ ID NO:1 consisting of mutations at positions 87, 96, 244, 247 or 248 of SEQ ID NO:1 or a variant of SEQ ID NO:24 consisting of mutations at positions 47, 51 or 87 of SEQ ID NO:24. However, the claimed method is drawn to making a genus of variants for which there is no teaching. There is no evidence on the record of the relationship between the structure of a P450Cam of SEQ ID NO:1 and the structure of any recombinants, variants and mutants of SEQ ID NO:1 and there is no evidence on the record of the relationship between the structure of a P450BM-3 of SEQ ID NO:24 and the structure of any recombinants, variants and mutants of SEQ ID NO:24. Therefore, the specification fails to describe a method of making a representative number of species of the genus comprising variants of P450cam or P450BM03 having any structure.

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Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 3, 5 and 22-24.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Claims 3, 5 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of a method of oxidizing limonene, pinene or cyclic sesquiterpene using a variant of SEQ ID NO:1 consisting of mutations at positions 87, 96, 244, 247 or 248 of SEQ ID NO:1 or a variant of SEQ ID NO:24 consisting of mutations at positions 47, 51 or 87 of SEQ ID NO:24, does not reasonably provide enablement for a method of oxidizing limonene, pinene or cyclic sesquiterpene using any or all variants, mutants and recombinants of SEQ ID NO:1 or 24 having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

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the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 3, 5 and 22-25 are drawn to a method of oxidizing limonene, pinene or cyclic sesquiterpenes with A) variants of a P450cam of SEQ ID NO:1, wherein said variant comprises one or more substitutions at positions 87, 96, 244, 247 or 248 of SEQ ID NO:1 or B) variants of a P450BM-3 of SEQ ID NO:24, wherein said variant comprises one or more substitutions at positions 47, 51, or 87 of SEQ ID NO:24.

Further, the claims are not limited to variants of SEQ ID NO:1 consisting of the substitutions at positions 87, 96, 244, 247 or 248, but to any variant of SEQ ID NO:1 comprising the recited substitutions and any other modifications. Similarly, the claims are not limited to variants of SEQ ID NO:24 consisting of the substitutions at positions 47, 51, or 87, but to any variant of SEQ ID NO:24 comprising the recited substitutions and any other modifications. Therefore, the claims are drawn to a method of oxidizing limonene, pinene or cyclic sesquiterpene using a polypeptides having any structure

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of producing an extremely large number of variants, mutants and recombinants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the

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ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of a method of oxidizing limonene, pinene or cyclic sesquiterpene using a variant of SEQ ID NO:1 consisting of mutations at positions 87, 96, 244, 247 or 248 of SEQ ID NO:1 or a variant of SEQ ID NO:24 consisting of mutations at positions 47, 51 or 87 of SEQ ID NO:24. It would require undue experimentation of the skilled artisan to make and use all the claimed variants, mutants and recombinants claimed herein. In view of the great breadth of the claim, amount of experimentation required to make and use the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of oxidizing limonene, pinene or cyclic sesquiterpene using any or



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all variants of SEQ ID NO:1 or 24 because the specification does not establish: (A)) regions of the polypeptide structure which may be modified without affecting P450 activity; (B) the general tolerance of P450 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; (D) a rational and predictable scheme for selecting P450 variants with an expectation of oxidizing the recited substituted derivatives of pinene, limonene and any cyclic sesquiterpenes; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of oxidizing limonene, pinene or cyclic sesquiterpene using any or all variants of SEQ ID NO:1 or 24 having any structure. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, variants of SEQ ID NO:1 or 24 having any structure, including any or all recombinants, mutant or variants, having the desired biological characteristics recited in the claim is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

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In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the claims are fully enabled because the claims have been amended to delete references homologous enzymes. Examiner respectfully disagrees. The claims are not limited to a method of using variants of SEQ ID NO:1 or 24 consisting of the above amino acid mutations, but a method of using any variant of SEQ ID NO:1 or 24 comprising the recited substitutions and any other modifications. The limitation of comprising substitutions at the recited amino acids of SEQ ID NO:1 or 24 provides no description on the structure of other parts of the variant. Therefore, the claims are drawn to a method of using variants of SEQ ID NO:1 or 24 having any structure, including any or all recombinants, mutants and variants of SEQ ID NO:1 or 24, including those that comprise the recited substitutions. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Hence the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 5 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al.

Claims 3, 5 and 22-25 are drawn to a method of oxidizing pinene, limonene or cyclic sesquiterpene or derivatives of said pinene, limonene or cyclic sesquiterpene using a variant of P450BM0-3 of SEQ ID NO:24 or P450Cam of SEQ ID NO:1 comprising of the recited amino acid mutations and/or any other amino acid mutations,

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wherein the resulting variant has a higher oxidation activity towards the substrate compared to wildtype P450cam of SEQ ID NO:1.

Wong et al. (UK Publication GB 2 294 692 A, UK Publication GB 2 306 485 A or U.S. Patent No. 6,117,661) disclose mutant P450cam having mutations at amino acid 87 and/or 96 of a P450cam (abstract and Columns 2-4 and 25-27). The P450cam of Wong et al. and the P450cam of SEQ ID NO:1 of the instant invention are 100% identical (see Sequence Alignment – cited previously on form PTO-892). Wong et al. disclose a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of P450<sub>CAM</sub>, fielding for new substrates (Columns 2 and 5-27). Sesquiterpenes and monoterpenes belong to the same family of molecules called terpenes, which contain the signature isoprene units. Since compounds similar in structure will have similar properties, one having ordinary skill in the art would have recognized to use the mutant P450 of Wong et al. to oxidize other terpenes, such as pinene, limonene and longifolene, a sesquiterpene. The mutant of Wong et al. inherently possesses the same material functional characteristics as the mutant P450 claims 3, 5 and 22-25 since both mutant P450 enzymes have mutations at amino acids 87 and/or 96.

Since the Office does not have facilities for examining and comparing applicant's mutant P450 enzyme with the mutant P450 enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the mutant P450 enzyme of the prior art does not possess the same material functional characteristics of the claimed mutant P450

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enzyme). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Such pinene, limonene and longifolene are commercially available through Sigma Catalog 1995, pages 624, 640 and 837) (form PTO-892).

Therefore, combining the teachings of the above two references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to oxidize other terpenes, such as pinene, limonene and longifolene using the method taught by Wong et al. One of ordinary skill in the art would have been motivated to oxidize other terpenes instead of chemically synthesizing oxidized products of said substrates. One of ordinary skill in the art would have had a reasonable expectation of success Wong et al. teaches a method of oxidizing terpenes using mutants of P450Cam and since the recited terpenes are commercially available through Sigma Catalog.

Therefore, Wong et al. and Sigma Catalog render claims 3, 5 and 22-25 *prima facie* obvious to those skilled in the art.

Claims 1-3, 5 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flitsch et al.

Claims 2-3, 5 and 22-25 are drawn to a method of oxidizing pinene, limonene or cyclic sesquiterpene or derivatives of said pinene, limonene or cyclic sesquiterpene using a variant of P450BM0-3 of SEQ ID NO:24 or P450Cam of SEQ ID NO:1 comprising of the recited amino acid mutations and/or any other amino acid mutations,

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wherein the resulting variant has a higher oxidation activity towards the substrate compared to wildtype P450cam of SEQ ID NO:1.

Flitsch et al. (US Patent 6,100,074 – cited previously on form PTO-892) disclose mutant P450cam having mutations at amino acid 87 and/or 96 of a P450cam (abstract and Columns 2-4 and 25-27). The P450cam of Flitsch et al. and the P450cam of SEQ ID NO:1 of the instant invention are 100% identical (see Sequence Alignment - form PTO-892). Flitsch et al. disclose a method of oxidizing various substrates, including monoterpenes and isoprenes, with mutant P450 enzymes of P450<sub>CAM</sub>, fielding for new substrates (Columns 2 and 25-27). ). Sesquiterpenes and monoterpenes belong to the same family of molecules called terpenes, which contain the signature isoprene units. Since compounds similar in structure will have similar properties, one having ordinary skill in the art would have recognized to use the mutant P450 of Flitsch et al. to oxidize other terpenes, such as pinene, limonene and longifolene, a sesquiterpene. Since compounds similar in structure will have similar properties, one having ordinary skill in the art would have recognized to use the mutant P450 of Flitsch et al. to oxidize other terpenes, such as pinene, limonene and longifolene, a sesquiterpene. The mutant mutant of Flitsch et al. inherently possesses the same material functional characteristics as the mutant P450 claims 2-3, 5 and 22-25 since both mutant P450 enzymes have mutations at amino acids 87 or 96.

Since the Office does not have facilities for examining and comparing applicant's mutant P450 enzyme with the mutant P450 enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the

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product of the prior art (i.e., that the mutant P450 enzyme of the prior art does not possess the same material functional characteristics of the claimed mutant P450 enzyme). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Such pinene, limonene and longifolene are commercially available through Sigma Catalog 1995, pages 624, 640 and 837) (form PTO-892).

Therefore, combining the teachings of the above two references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to oxidize other terpenes, such as pinene, limonene and longifolene using the method taught by Flitsch et al. One of ordinary skill in the art would have been motivated to oxidize other terpenes instead of chemically synthesizing oxidized products of said substrates. One of ordinary skill in the art would have had a reasonable expectation of success Flitsch et al. teaches a method of oxidizing terpenes using mutants of P450Cam and since the recited terpenes are commercially available through Sigma Catalog.

Therefore, Flitsch et al. and Sigma Catalog render claims 3, 5 and 22-25 *prima facie* obvious to those skilled in the art.

In response to the previous Office Action, applicants have traversed the above rejections together.

Applicants state that the subject matter related to P450BM-3 mutant enzymes appear to be non-obvious from Examiner comments, and therefore, the only

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outstanding issue relates to the subject matter relating to P450CAM mutant enzymes. Examiner disagrees. Subject matter related to P450BM-3 mutant enzymes were never indicated as non-obvious by Examiner. Since the claims are drawn to a method of using P450BM-3 mutant enzymes or P450CAM mutant enzymes, the cited references in combination teach all embodiments of the claims.

Applicants argue that since Wong and Flitsch do not disclose testing limonene, pinene or a cyclic sesquiterpene of the present claims or provide any teaching for predicting which substrate would be oxidized by mutant P450cam enzymes, a skilled artisan would not be motivated to test a limonene, pinene or a cyclic sesquiterpene. Examiner respectfully disagrees. As applicants have stated, Wong and Flitsch disclose results from the testing of a large number of compounds, including terpenes, such as an isoprene. Even though an isoprene is smaller than the recited substrates, the cited references discuss introducing less polar amino acids into the active site of the P450cam or even amino acids of different size to accommodate large substrates, compounds larger than sesquiterpenes (Columns 5-27 of Wong et al. and Columns 5-27 of Flitsch et al.). Therefore, one of ordinary skill in the art would have had a reasonable expectation of oxidizing large substrates, such as large terpenes, like sesquiterpenes. Further, since compounds similar in structure will have similar properties, the ability of the mutant P450 enzymes of Wong et al. or Flitsch et al. to act on other terpenes would not have been an unexpected result or totally unpredictable.

Applicants also argue that the in the declaration filed with the previous response, discusses that a person of ordinary skill in the art would not have proceeded to test the



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cited substrates because one of ordinary skill in the art would need to assess whether an active site known to oxidize small molecules or flat planar aromatic molecules would be expected to oxidize large molecules. Examiner disagrees. Examiner respectfully disagrees. As applicants have stated, the cited references discuss introducing less polar amino acids into the active site of the P450cam or even amino acids of different size to accommodate large substrates. Also, the cited references use larger molecules than sesquiterpenes as substrates for the P450 mutants (Columns 5-27 of Wong et al. and Columns 5-27 of Flitsch et al.). Therefore, one of ordinary skill in the art would have had a reasonable expectation of oxidizing larger terpenes, such as sesquiterpenes. Further, since compounds similar in structure will have similar properties, the ability of the mutant P450 enzymes of Wong et al. or Flitsch et al. to act on other terpenes would not have been an unexpected result.

Applicants also argue that the cited reference do not disclose or suggest mutant P450 having multiple mutations have higher levels of oxidation. Examiner respectfully disagrees. Wong and Flitsch both disclose P450cam mutants having F87 and F96 mutations (Columns 2-4 and 25-27). The property of having higher oxidation activity for the recited substrates, since the Office does not have facilities for examining and comparing applicant's mutant P450 enzyme with the mutant P450 enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the mutant P450 enzyme of the prior art does not possess the same material functional characteristics of the

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claimed mutant P450 enzyme). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Applicants argue that Examiner's statement of "one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions" supports that the skilled person would expect mutations in the active site to disrupt or diminish oxidation activity, providing evidence of the fact that the person of ordinary skill in the art would have no reason to assume that multiple mutations would provide increased activity. Examiner respectfully disagrees. Wong and Flitsch discloses which specific amino acids of P450cam to mutate, wherein its oxidation activity is not disrupted (Columns 25-27). Even though Wong and Flitsch do not test the recited substrates, it would have been obvious to one having ordinary skill in the art to test other substrates. Also, since the Office does not have facilities for examining and comparing applicant's mutant P450 enzyme with the mutant P450 enzyme of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the mutant P450 enzyme of the prior art does not possess the same material functional characteristics of the claimed mutant P450 enzyme). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

None of the claims are allowable.

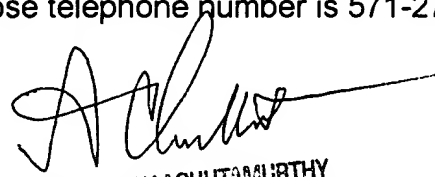
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak  
Patent Examiner 1652



PONNATHAPU ACHUTAMURTHY  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600